DRAFT

REMARKS

I. Claim Status. Claims 2, 5, 28, 48, and 50 have been amended. Claim 51 has been added. Support for these amendments can be found in the specification according to the following:

claim 2- at page 14 line 35, to page 15, line 3; and page 19, lines 15-18;

claim 5-at page 3, lines 12-16;

claim 28-at page 44, lines 10-13; and

claim 50 and claim 51-at page 27, lines 22-32.

Claims 50 has been amended for clarity, but otherwise recites the same subject matter as the previous version of the claim. Accordingly, no new matter has been added to the claim.

Each amendment being supported by the application as filed, the amendments to claims 2, 5, 28, 48 and 50 and the addition of claim 51 do not add new matter to the specification.

By this amendment, claims 2-14, 16-34 and 40-51 are pending.

II. Specification. As requested by the Examiner, the specification has been amended to make reference to the color drawings shown in Figure 10. No new matter has been introduced by this process.

III. Claim Objections. Claims 48 and 50 have been objected to for containing informalities. Claim 48 has been amended to insert the word "structure," as requested by the Examiner. The form of claim 50 has been amended to clarify the sets of amino acid substitutions

of the recombinant allergen that are recited in the claim. Applicants respectfully submit that the objections to claims 48 and 50 have been addressed and overcome. Reconsideration of claims 48 and 50 is respectfully requested.

IV. Claim Rejections.

(i) Claims rejected under 35 U.S.C. §112, first paragraph. Claims 2-14, 32-34 and 47-50 have been rejected for lack of enablement because the Examiner contends that the specification does not reasonably enable the full scope of the claims. Applicants respectfully disagree.

Enclosed herewith is a Declaration under 37 C.F.R. § 1.132 of Dr. T.P. King, an Associate Professor at the Rockefeller University, and head of the Laboratory of Biochemistry. Dr. King's research focuses on elucidating the immunogenic regions on allergens responsible for causing IgE-mediated allergic reactions in susceptible individuals, based on common structural features and antigenic cross-reactivity with other proteins in the environment.

Contrary to the Examiner's position, and based on his expertise and experience and knowledge of the field of allergen structure and immunotherapy, Dr. King confirms that, at the time the invention was made, the specification provides sufficient support to enable one of ordinary skill in the art to make and use the claimed recombinant mutant allergens, having the desired characteristics described therein, using any known allergen, based on the structural similarity of homologous proteins. In addition to his own experience, Dr. King provides three references which demonstrate the state of the art prior to and as of the filing date of the

application with respect to (i) predicting the structural similarity of homologous proteins; (ii) constructing three-dimensional models of allergen protein structure; and (iii) identifying specific amino acid residues within B cell epitopes involved in antibody binding based on three-dimensional structures.

As set forth in Dr. King's declaration, the specification explicitly presents four conditions that must be met to obtain mutant recombinant allergens that are useful as vaccines against IgE-mediated allergic reactions: (i) the amino acid residue targeted for mutation must be one that is highly conserved among homologues and must be within a region that is also highly conserved (*e.g.*, having significant percent identity); (ii) the amino acid residue must be within a B-cell epitope and, thus, must be surface-exposed; (iii) the mutation must not disrupt the α-carbon backbone tertiary structure of the allergen; and (iv) the mutation must decrease IgE binding relative to the wild-type allergen. The specification at pages 19-20 further provides a detailed description of the quantitative criteria used to obtain the mutant allergens, having the above characteristics (*i.e.*, identifying a residue in a protein having more than 70% identity with that of a known allergen that is at least 20% solvent-accessible and is within a conserved region greater than 400Å^2, then making a non-conservative residue substitution that results in a less than 2Å deviation of the root mean square of the atomic coordinates of the molecule). As set forth by Dr. King and as supported by the accompanying evidentiary references, determination of these criteria was well-known and routine to those skilled in the art at the time the invention was made.

As set forth by Dr. King, no later than March 18, 1998, there existed numerous means for predicting specific amino acid residues that are conserved among homologous

proteins, the substitution of which would not alter the α-carbon tertiary structure. Such homologous proteins always have structural similarity. Accordingly, given an amino acid sequence of a naturally occurring allergen of interest, homologues would be readily identifiable using any comparative database for sequence alignment (see specification at page 4, lines 23-35) and consequently, highly conserved regions comprised of residues having a high percent identity would be readily identifiable. Further, determining the known three-dimensional structure of even one homologous protein within a group would provide guidance as to which amino acid residues were buried within the hydrophobic interior of the protein, thus providing in the α-carbon backbone, and therefore, would not be candidates for mutation. Similarly, determination of the structure would provide guidance as to which conserved residues were surface-localized and solvent exposed (*i.e.*, good candidates for mutation). As set forth in the specification at page 19, lines 10-11 and in paragraph 8 of Dr. King's Declaration, numerous and routine techniques for predicting the relationship between sequences of homologous proteins and their corresponding tertiary structures were known to those of ordinary skill in the art at the time the invention was made. Hence, contrary to the Examiner's position, at the time the invention was made, based on the disclosure of the application and using routine techniques, one of ordinary skill in the art could determine which amino acids and the specific type of amino acid within the full-length amino acid sequence of any recombinant allergen could be substituted without altering the α-carbon backbone tertiary structure of the allergen.

Dr. King's Declaration also sets forth that, in view of the state of the art of predicting B cell epitopes and contrary to the Examiner's position, it would not require undue

experimentation to substitute amino acid residues that are directly involved in antibody binding within B cell epitopes (*i.e.*, the functional epitope) which would reduce the affinity of binding between the allergen and the IgE. The ordinarily skilled immunologist readily would have been able to identify the epitopes based on their conservation and sequence identity with other cross-reactive proteins, and by their surface localization within the three-dimensional structure of the protein. As discussed above, knowledge of the structure of even one homologue within a group of homologous allergen permits identification of corresponding residues on other homologous proteins. At the time the invention was made, the skilled practitioner would have been able to identify the relatively few specific residues within the epitopes that directly interact with the antibody (*i.e.*, form chemical bonds) using available techniques such as X-ray diffraction of Fab' and/or Fv complexes with antigen, with such precision as to identify the specific nature and number of the chemical bonds forming the interaction. Alternatively, candidates for mutation could be predicted based on the criteria described in the specification, since residues meeting that criteria are likely contained within antigenic epitopes (page 19, line 30, to page 20, line 2) and not within the α-carbon backbone. Tests for evaluating binding affinity of resultant mutated allergens are described in detail in the Examples (*e.g.*, page 31, lines 24-35 and Figure 4). Thus, contrary to the Examiner's contention, it would not be unduly difficult for one of ordinary skill in the art to predict the three-dimensional structure of modified allergens and assess reduced binding to IgE for allergens other that Bet v I.

The Examiner has also objected to the term "comprises" atoms of 15-25 amino acid residues. In response, claim 5 has been amended to recite that the patch consists of at least

15 amino acid residues. New dependent claim 51 recites that the patch consists of 15-25 amino acids. Applicants direct the Examiner's attention to the specific limitations of the claim, in particular that the residues must be those having at least 70% identity with all known homologous proteins and solvent accessibility (defined as the area accessible to a sphere with a radius comparable to 1.4Å) of at least 20%, and be within a conserved patch of at least 400Å^2. Hence, the amended claims clearly set forth the metes and bounds of the claim with respect to both the number and characteristics of the patch.

With respect to claims directed to a pharmaceutical composition comprising a mutant recombinant allergen for use as a vaccine for treating allergies, the Examiner contends that it is "inconceivable" that any recombinant allergen obtained according to the teachings of the application would be useful as a pharmaceutical or vaccine in the absence of *in vivo* data. The Examiner asserts the position that even if IgE binding is reduced by 5-10%, there is still a 90-95% chance that the mutant will bind IgE. Applicants respectfully disagree with the Examiner's postition.

Applicants maintain their previous arguments regarding the claimed pharmaceutical compositions. U.S. patent law dictates that the requirements of Section 112 are met when there is an established correlation between the *in vitro* assays and a disclosed method of use. An *in vitro* example in the specification constitutes a "working example" if there is an established correlation between the *in vitro* assay and the disclosed method of use, and should be accepted as correlating unless the Examiner has evidence that the model does not correlate. To establish the latter, the Examiner also must decide whether one skilled in the art would accept the model as

reasonably correlating [*In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)]. Applicants maintain that the specification contains several detailed examples of *in vitro* data which clearly establish a correlation between the *in vitro* effects of reduced IgE binding, as evidenced using *ex vivo*-derived serum from allergic individuals, and use as a therapeutic vaccine when administered *in vivo*. As discussed extensively in the specification at page 3, line 27, to page 10, line 16, allergy vaccination is well known in the art, and includes the practice of amino acid substitution to ameliorate the unwanted effects of IgE-binding which occurs during the ongoing immune response.

Hence, it cannot be "inconceivable" that the recombinant allergen described in the instant application, which contains substituted amino acid residues similar to the vaccines referenced-above, and further is designed to mitigate an IgE-mediated allergic response by initiating a *B-cell-mediated* T-cell (Th1) protective immune response (page 12, lines 13-23), would have use as a therapeutic, and would have been recognized as having such a use by those skilled in the art.

For the reasons set forth above, Applicants respectfully submit all rejections under 35 U.S.C. §112, first paragraph have been addressed and overcome. Reconsideration of the claims and withdrawal of all rejections under 35 U.S.C. §112, first paragraph is respectfully requested.April 3, 2002

(ii) Rejections under 35 U.S.C. §112, Second Paragraph. Claims 2-14, 16-28, 32-34 and 47-50 have been rejected as indefinite. In response, the claims have been amended as follows: 1. In claims 2 and 48, the term "essentially" has been deleted and the term "preserved"

has been replaced with "conserved". This change is supported in the specification at page 19, lines 15-18. 2. Claim 28 has been amended to further clarify the claimed amino acid substitutions, as suggested by the Examiner, although Applicants submit that the original format is standard within the art and not ambiguous.

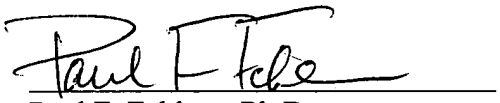
Applicants respectfully submit all rejections under 35 U.S.C. §112, second paragraph have been addressed and overcome. Reconsideration of the claims and withdrawal of all rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

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PATENT TRADEMARK OFFICE

Docket No: 4305/1E144-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hans Henrik Ipsen; Michael Dho Spangfort; Jorgen Nedergaard Larsen

Serial No.: 09/270,910 Art Unit: 1644

Confirmation No.:

Filed: 3/16/99 Examiner: P. Huynh

For: NOVEL RECOMBINANT ALLERGENS

MARK-UP FOR AMENDMENT PURSUANT TO 37 C.F.R. § 1.121

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

April 10, 2002

Sir:

IN THE SPECIFICATION:

On the "Brief Description of the Drawings,", the description of Figure 10 that begins at page 11, line 23 has been amended as follows:

Figure 10 is a color drawing that shows solvent accessability of individually aligned antigen 5

residues and alignment of *Vespula* antigen 5 sequences (left panel). On the right panel of Figure 10 is shown the molecular surface of antigen 5 with conserved areas among *Vespula* antigen 5:s.

IN THE CLAIMS:

Claims 2, 5, 28, 48 and 50 have been amended as follows:

2. (Thrice Amended) A recombinant allergen according to claim 48, obtainable by

a) identifying amino acid residues in a naturally occurring allergen which are conserved with more than 70% identity in all known of the homologous proteins within the taxonomic order from which said naturally occurring allergen originates;

b) defining at least one patch of conserved amino acid residues being coherently connected over at least 400 $Å^2$ of the surface of the three-dimensional structure of the naturally occurring allergen molecule as defined by having a solvent accessibility of at least 20%, said at least one patch comprising at least one B cell epitope; and

c) substituting at least one amino acid residue in said at least one patch with another non-conservative amino acid [which is not conserved], wherein the α-carbon backbone tertiary structure of the allergen molecule is [essentially preserved] conserved.

5. (Thrice Amended) A recombinant allergen according to claim 2, wherein said at least one patch [comprises atoms of] consists of at least 15[-25] amino acid residues.

28. (Thrice Amended) A recombinant allergen according to claim 25, wherein the substitution is [Lys72A1a or Tyr96A1a] from Lys to Ala at position 72 or from Tyr to Ala at position

96.

48. (Amended) A recombinant mutant allergen derived from a naturally occurring allergen in which at least one surface-exposed, amino acid residue of a B cell epitope at a position which is conserved in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates, is substituted with an amino acid residue which is not conserved in the same position in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates, wherein the [recombinant mutant allergen has an] α-carbon backbone tertiary structure of the recombinant allergen [essentially the same as] is conserved as compared with the α-carbon backbone tertiary structure of the naturally occurring allergen, and specific IgE binding to the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen.

50. (Amended) A recombinant allergen according to claim 14 wherein said allergen has one or more [an] amino acid substitutions selected from the group consisting of:

(i) Thr [substituted] at position 10 of SEQ ID NO: 37 substituted with Pro[,];

(ii) Asp [substituted] at position 25 of SEQ ID NO: 37 substituted with Gly[,];

(iii) [(]Asn [substituted] at position 28 of SEQ ID NO: 37 substituted with Thr[,] and Lys [substituted] at position 32 of SEQ ID NO: 37 substituted with Gln[),];

(iv) Glu [substituted] at position 45 of SEQ ID NO: 37 substituted with Ser[,];

(v) Asn [substituted] at position 47 of SEQ ID NO: 37 substituted with Ser[,];

(vi) Lys [substituted] at position 55 of SEQ ID NO: 37 substituted with Asn[,];

(vii) Thr [substituted] at position 77 of SEQ ID NO: 37 substituted with Ala[,];

(viii) Pro [substituted] at position 108 of SEQ ID NO: 37 substituted with Gly[,]; [or] and

(ix) Asp [substituted] at position 28 of SEQ ID NO: 37 substituted with Thr, Lys [substituted] at position 32 of SEQ ID NO: 37 substituted with Gln, Glu [substituted] at position 45 of SEQ ID NO: 37 substituted with Ser, Pro [substituted] at position 108 of SEQ ID NO: 37 substituted with Gly[)].